Drug Class Review
on
Calcium Channel Blockers

Update #3: Preliminary Scan Report 2

December 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:
Original Final Report March 2005 (searches through February 2004)

Date of Last Update Scan:
December 2006

SCOPE AND KEY QUESTIONS:

The purpose of this review is to compare the benefits and harms of calcium channel blockers when used to treat hypertension, supraventricular arrhythmias, angina or .left ventricular dysfunction. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. Do CCBs differ in effectiveness in the treatment of adult patients with essential hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (left ventricular ejection fraction [LVEF] <45%)?
2. Do CCBs differ in their safety or adverse effects in the treatment of adult patients with essential hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (LVEF<45%)?
3. Based on demographics (age, racial groups, gender), other medications, or comorbidities, are there subgroups of patients for which one CCB is more effective or is associated with fewer adverse effects?

Inclusion Criteria

Population

Adults with hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmia or supraventricular tachycardia (SVT), and systolic dysfunction (LVEF <45%).

Interventions

Amlodipine
Bepridil
Diltiazem
Felodipine
Isradipine
Nicardipine
Nifedipine
Nisoldipine
Verapamil

Outcomes

Hypertension
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Development of renal failure (end stage renal disease/dialysis/transplant/ clinically significant, permanent increase in serum creatinine or decrease in creatinine clearance)
Quality of Life

Angina
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Symptoms
Quality of Life

Supraventricular Arrhythmias
All cause mortality
Cardiovascular (CV) disease mortality
Stroke
Symptoms (rate or rhythm control)
Quality of Life

Left-ventricular Dysfunction
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Symptoms
Quality of Life

METHODS

Literature Search

To identify new potentially relevant citations, we searched MEDLINE (December 2006 to December 2007). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 84 citations. Of those, there are 3 new potentially relevant controlled clinical trials (Appendix A). Two of these are further analyses of the previously included trials, INVEST and ACTION. Taken together with the 24 trials identified in the first preliminary update scan, now there are a total of 27.

New Drugs
None

New Indications
None

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New Safety Alerts
New information was added to the 'Precautions' section of the product labels for 4 CCB's. Details of these changes are listed in the table below.

CCB	Date of change	Details of new 'Precautions' information
Cardizem LA (diltiazem hydrochloride) Extended Release Tablets	4/07	Drug Interactions: Bispirone , Quinidine Buspirone: In 9 healthy subjects, diltiazem significantly increased the mean buspirone AUC5.5-fold and c-max 4.1 fold compared to placebo. The t ½ and Tmax of buspirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during coadministration and should be based on clinical assessment Quinidine: Diltiazem significantly increases the AUC 0-∞ of quinidine by 51%, t½ by 36% and decreases it's CL_{oral} by 33%. Monitoring of quinidine adverse effects may be warranted and the dose adjusted accordingly.

CCB	Date of change	Details of new 'Precautions' information
Tiazac (diltiazem hydrochloride) Extended-Release Capsules	6/07	Drug Interactions: Bispirone , Quinidine Buspirone: In 9 healthy subjects, diltiazem significantly increased the mean buspirone AUC5.5-fold and c-max 4.1 fold compared to placebo. The t ½ and Tmax of buspirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during coadministration and should be based on clinical assessment Quinidine: Diltiazem significantly increases the AUC 0-∞ of quinidine by 51%, t½ by 36% and decreases it's CLoral by 33%. Monitoring of quinidine adverse effects may be warranted and the dose adjusted accordingly.
Verelan PM (verapamil hydrochloride) Extended-Release Capsules Controlled Onset	5/07	Drug Drug Interactions Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent telithromycin, an antibiotic in the ketolide class of antibiotics
Cardene I.V. (nicardipine hydrochloride)	6/07	Geriatric Use: The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (>65 years) and young healthy adults. Clinical studies of nicardipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

APPENDIX A

Cooper-DeHoff, R. M., Q. Zhou, et al. (2007). "Influence of Hispanic ethnicity on blood pressure control and cardiovascular outcomes in women with CAD and hypertension: findings from **INVEST**." Journal of Women's Health **16**(5): 632-40.

BACKGROUND: Prospective data regarding blood pressure (BP) control and cardiovascular (CV) outcomes in Hispanic women are lacking. METHODS: We analyzed 5017 Hispanic and 4710 non-Hispanic white hypertensive women with coronary artery disease (CAD) in the INternational VErapamil SR/Trandolapril STudy (INVEST) to determine the impact of baseline characteristics and BP control on CV outcomes. RESULTS: At baseline, Hispanic women were younger and a had lower prevalence of most established CV risk factors than non-Hispanic white women. At 24 months, BP control (< 140/90 mm Hg) was achieved in 75% of Hispanic and 68% of non-Hispanic white women, ($p < 0.001$), with most women, regardless of ethnicity, requiring > or =2 antihypertensive agents. Following 26,113 patient-years of follow-up, the primary outcome (first occurrence of nonfatal myocardial infarction [MI], nonfatal stroke, or all cause death) occurred in 5.7% of Hispanic and 12.3% of non-Hispanic white women (adjusted HR = 0.84, 95% CI = 0.71-0.98, $p = 0.03$). There was no difference in outcome in either group of women comparing the randomized antihypertensive treatment strategies. CONCLUSIONS: Despite accounting for a lower risk profile, deployment of protocol-based antihypertensive treatment regimens resulted in superior BP control and fewer CV events in Hispanic women compared with non-Hispanic white women.

Ruilope, L. M., B.-A. Kirwan, et al. (2007). "Uric acid and other renal function parameters in patients with stable angina pectoris participating in the **ACTION** trial: impact of nifedipine GITS (gastro-intestinal therapeutic system) and relation to outcome." Journal of Hypertension **25**(8): 1711-8.

BACKGROUND: Little data is available concerning the prognostic implications of renal function abnormalities, their evolution over time and the effects of nifedipine on such abnormalities in patients with stable angina pectoris. METHODS: The previously published ACTION trial compared long-acting nifedipine GITS 60 mg once daily to placebo among 7,665 patients. Standard laboratory tests including creatinine and uric acid were assessed at baseline, after 6 months, 2 and 4 years, and at the end of follow-up. We assessed the impact of nifedipine on markers of renal dysfunction and determined whether evidence of renal failure alters the impact of nifedipine on the clinical outcome of patients with stable angina. RESULTS: Uric acid was not while creatinine level and estimated creatinine clearance were potent conditionally independent predictors of total mortality and of cardiovascular clinical events. Relative to placebo, nifedipine reduced 6-month uric acid levels by 3% ($P < 0.001$) of the baseline value. This difference was maintained during long-term follow-up, was present both in normotensives and in hypertensives, and was not explained by differences in diuretic therapy or allopurinol use. Nifedipine had no effect on the occurrence of clinical renal failure. Relative to placebo, the effects of nifedipine on cardiovascular death or myocardial infarction [hazard ratio (HR) = 1.01, 95% confidence interval (CI) 0.88-1.17], any stroke or transient ischaemic attack (HR = 0.73, 95% CI 0.60-0.88), new overt heart failure (HR = 0.72, 95% CI 0.55-0.95), and the need for any coronary procedure (HR = 0.81, 95% CI 0.75-0.88) were consistent across strata of markers of renal dysfunction. CONCLUSIONS: We conclude that, in patients with stable angina, nifedipine reduces uric acid levels and does not affect other markers of renal dysfunction. Renal dysfunction does not alter the effects of nifedipine on clinical outcome.

Ruzyllo, W., M. Tendera, et al. (2007). "Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial." Drugs **67**(3): 393-405.

BACKGROUND AND OBJECTIVE: Current medical therapies for the symptoms of angina pectoris aim to improve oxygen supply and reduce oxygen demand in the myocardium. Not all patients respond to current antianginal monotherapy, or even combination therapy, and a new class of antianginal drug that complements existing therapies would be useful. This study was undertaken to compare the antianginal and anti-ischaemic effects of the novel heart-rate-lowering agent ivabradine and of the calcium channel antagonist amlodipine. PATIENTS AND METHODS: Patients with a >/=3-month history of chronic, stable effort-induced angina were randomised to receive ivabradine 7.5mg (n = 400) or 10mg (n = 391) twice daily or amlodipine 10mg once daily (n = 404) for a 3-month, double-blind period. Bicycle exercise tolerance tests were performed at baseline and monthly intervals. The primary efficacy criterion was the change from baseline in total exercise duration after 3 months of treatment. Secondary efficacy criteria included changes in time to angina onset and time to 1mm ST-segment depression, rate-pressure product at trough drug activity, as well as short-acting nitrate use and anginal attack frequency (as recorded in patient diaries). RESULTS: At 3 months, total exercise duration was improved by 27.6 +/- 91.7, 21.7 +/- 94.5 and 31.2 +/- 92.0 seconds with ivabradine 7.5 and 10mg and amlodipine, respectively, both ivabradine groups were comparable to amlodipine (p-value for noninferiority < 0.001). Similar results were observed for time to angina onset and time to 1mm ST-segment depression. Heart rate decreased significantly by 11-13 beats/min at rest and by 12-15 beats/min at peak of exercise with ivabradine but not amlodipine, and rate-pressure product decreased more with ivabradine than amlodipine (p-value vs amlodipine <0.001, at rest and at peak of exercise). Anginal attack frequency and short-acting nitrate use decreased substantially in all treatment groups with no significant difference between treatment groups. The most frequent adverse events were visual symptoms and sinus bradycardia with ivabradine (0.8% and 0.4% withdrawals, respectively) and peripheral oedema with amlodipine (1.5% withdrawals). CONCLUSIONS: In patients with stable angina, ivabradine has comparable efficacy to amlodipine in improving exercise tolerance, a superior effect on the reduction of rate-pressure product (a surrogate marker of myocardial oxygen consumption) and similar safety.